IN THE SPECIFICATION

Please replace the paragraph bridging pages 11 and 12 with the following new paragraph:

The subject invention provides a substantially isolated or purified chitinase, said chitinase being a human chitinase having an amino acid sequence essentially corresponding to the amino acid sequence shown in fig. 1 (SEQ ID NO:4) or the amino acid sequence shown in fig. 2 (SEQ ID NO:6), or being a modified form of said human chitinase having a substantially similar chitin-hydrolyzing activity. It is preferred that this new human chitinase is produced by a genetically engineered host cell and isolated from said host cell or medium in which said host cell is cultured, wherein the amino acid sequence of the enzyme is encoded by a nucleotide sequence essentially corresponding to the nucleotide sequence shown in fig. 1 (SEQ ID NO:3) or the nucleotide sequence shown in fig. 2 (SEQ ID NO:5). The subject invention particularly includes a chitinase having an amino acid sequence essentially corresponding to the amino acid sequence shown in fig. 1 (SEQ ID NO:4) and having a molecular weight of about 50 kDa, and a chitinase having an amino acid sequence essentially corresponding to the amino acid sequence shown in fig. 2 (SEQ ID NO:6) and having a molecular weight of about 39 kDa.

Please replace the paragraph bridging pages 12 and 13 with the following new paragraph:

The phrase "essentially corresponding to" intends to allow for small sequence variations, such as the naturally occurring variations which do not significantly affect the activity of the enzyme. Some amino acids of the human chitinase sequence may be replaced by others, or be deleted, without thereby significantly affecting the function, activity and tolerability of the enzyme, and may sometimes even improve one characteristic or the overall properties of the enzyme. Generally, such sequence variations will be quite limited, say to about less than 30%, more often less than 20% or even less than 10% of all amino acids, i.e. the variants will generally have a high homology of above 70%, more often above 80% or

even above 90%, compared to the sequences shown in figs. 1 and 2 (SEQ ID NOs: 4 and 6). All have in common the functional characteristic of chitinase activity, which can be measured for typical chitinase substrates, such as 4-methylumbelliferyl-chitotrioside.

Please replace the paragraph on page 13, starting at line 6, with the following new paragraph:

The phrase "a modified form of said human chitinase having a substantially similar chitin-hydrolyzing activity" intends to embrace variants whose amino acid sequence differs significantly from the sequences shown in figs. 1 and 2 (SEQ ID NO:4 and 6) but which yet have a similar chitinase activity. Such modified forms having similar or even improved properties could be designed on the basis of the module or domain structure of the human chitinase, such as constructs lacking a domain which is not required or even disadvantageous for activity, and constructs containing two or more copies of a domain whose amplified presence is desirable.

Please replace the paragraph on page 13, starting at line 16, with the following new paragraph:

The phrase "having a substantially similar chitin-hydrolyzing activity" intends to set the minimum requirement of having an at least equivalent chitinase activity compared to the human chitinases shown in figs. 1 and 2 (SEQ ID NO:3-6). "Equivalent" refers to equivalency in substrate range, i.e. qualitatively, and to equivalency in activity value, i.e. quantitatively.

Please replace the paragraph on page 14, starting at line 12, with the following new paragraph:

The subject invention also provides a process for preparing a human chitinase having an amino acid sequence essentially corresponding to the amino acid sequence shown in fig. 1 (SEQ ID NO:4) or the amino acid sequence shown in fig. 2 (SEQ ID NO:6), or a modified

form of said human chitinase having a substantially similar chitin-hydrolyzing activity, comprising growing a genetically engineered host or host cell capable of producing said human chitinase or modified form thereof and isolating the chitinase produced from said host or host cell or from medium in which said host cell is cultured. In this process, preferably the amino acid sequence of said chitinase is encoded by a nucleotide sequence essentially corresponding to the nucleotide sequence shown in fig. 1 (SEQ ID NO:3) or the nucleotide sequence shown in fig. 2 (SEQ ID NO:5).

Please replace the paragraph on page 14, starting at line 25, with the following new paragraph:

The invention also provides a genetically engineered host cell capable of producing a human chitinase having an amino acid sequence essentially corresponding to the amino acid sequence shown in fig. 1 (SEQ ID NO:4) or the amino acid sequence shown in fig. 2 (SEQ ID NO:6), or a modified form of said human chitinase having a substantially similar chitin-hydrolyzing activity.

Please replace the paragraph on page 14, starting at line 31, with the following new paragraph:

This invention also provides a recombinant nucleic acid comprising a nucleotide sequence encoding, or complementary to a nucleotide sequence encoding, an amino acid sequence essentially corresponding to the amino acid sequence shown in fig. 1 (SEQ ID NO:4) or the amino acid sequence shown in fig. 2 (SEQ ID NO:6). Preferably, said nucleotide sequence essentially corresponds to, or essentially is complementary to, the nucleotide sequence shown in fig. 1 (SEQ ID NO:3) or the nucleotide sequence shown in fig. 2 (SEQ ID NO:5).

Please replace the paragraph on page 15, starting at line 1, with the following new paragraph:

The phrase "essentially complementary to" intends to cover all variants which can bind by hybridisation to the nucleotide sequences shown in figs. 1 and 2 (SEQ ID NOS:3 and 5), especially under stringent hybridisation conditions. The phrase "essentially corresponds to" intends to embrace all variants coding for the same or an equivalent (as to chitinase activity) amino acid sequence and being expressible by a host or host cell.

Please replace the paragraph on page 15, starting at line 8 with the following new paragraph:

The invention also embraces oligonucleotides of at least about 8 nucleotides having a nucleotide sequence corresponding to, or complementary to, a nucleotide sequence shown in fig. 1 (SEQ ID NO:3) or a nucleotide sequence shown in fig. 2 (SEQ ID NO:5) and being capable of binding by hybridisation under stringent (i.e. requiring about complete complementarity) hybridisation conditions to nucleic acid coding for the new human chitinase. Such oligonucleotides can be useful for different purposes, e.g. as a primer for use in nucleic acid amplification methods such as PCR, NASBA etc., or as a probe in hybridisation analysis. The length will usually depend on the intended use. When used as a primer, the length will normally be between 12, preferably 15, and 25, preferably 20 nucleotides. When used as a probe, the length will usually be somewhat higher, e.g. from about 15 or 20 up to about 40 or 50 nucleotides, or even up to the complete length of the coding sequence.

Please replace the paragraph on page 15, starting at line 24 with the following new paragraph:

Similarly, this invention furthermore embraces peptides of at least about 8 amino acid residues having an amino acid sequence derived from the amino acid sequence shown in fig. 1 (SEQ ID NO:4) or the amino acid sequence shown in fig. 2 (SEQ ID NO:6) and representing or mimicking an epitope of the new human chitinase, in particular those having an amino acid sequence corresponding to an amino acid sequence shown in fig. 1 (SEQ ID NO:4) or an amino acid sequence shown in fig. 2 (SEQ ID NO:6) and having antigenicity.

Usually, such peptides will have a length of at least about 10, or even at least about 15 amino acid residues, and up to about 40, preferably up to about 30 amino acid residues. Said peptides can be used for diagnostic purposes, or in immunization protocols to raise human chitinase-specific antibodies.

Please replace the paragraph on page 16, starting at line 18 with the following new paragraph:

Figure 1. Nucleotide sequence of chi.50 cDNA clone (SEQ ID NO:3) and predicted amino acid sequence of corresponding protein (SEQ ID NO:4).

Please replace the paragraph on page 16, starting at line 20 with the following new paragraph:

Figure 2. Nucleotide sequence of chi.39 cDNA clone (SEQ ID NO:5) and predicted amino acid sequence of corresponding protein (SEQ ID NO:6).

Please replace the paragraph on page 16, starting at line 24 with the following new paragraph:

Figure 4. Alignment of putative active site regions in some members of the chitinase protein family (SEQ ID NO:7-17).

Please replace the paragraph on page 27, starting at line 10 with the following new paragraph:

In order to clone cDNA encoding human chitotriosidase the following strategy was used. Chitotriosidase was purified from spleen of a type 1 Gaucher disease patient since this organ is extremely rich in chitotriosidase activity (18). The N-terminal amino acid sequence of chitotriosidase was determined and this information was used for cloning chitotriosidase cDNA. Firstly, the established N-terminal amino acid sequence of chitotriosidase (18) was

used to design a degenerate sense oligonucleotide: 5'-TGYTAYTTYACNAAYTGGGC-3' (SEQ ID NO:1). Secondly, a degenerate anti-sense nucleotide was designed based on the highly conserved domain among chitinases that is presumed to be an essential part of the catalytic center: 5'-CCARTCIARRTYIACICCRTCRAA-3' (SEQ ID NO:2).

Please replace the paragraph bridging pages 28 and 29 with the following new paragraph:

The nucleotide sequence (SEQ ID NO:3) of the cDNA clone chi.50 shows an open reading frame starting with an ATG at position 13 and ending with a TGA codon at position 1410 (see FIG.1). The open reading frame encodes a protein with a characteristic N-terminal ER signal peptide, immediately followed by the N-terminal sequence established for the chitotriosidase protein. The cDNA sequence does not indicate the presence of potential N-linked glycosylation sites, which is consistent with the absence of N-linked glycans in isolated chitotriosidase. The predicted protein, after removal of the signal sequence, has a length of 445 amino acids and a calculated molecular mass of 49 kDa. Metabolic labelling experiments with cultured macrophages revealed that these cells predominantly synthesize and secrete a chitotriosidase protein with apparent molecular mass of 50 kDa with polyacrylamide gel electrophoresis in the presence of sodium dodecylsulphate at reducing conditions. The predicted C-terminal part of 50 kDa human chitotriosidase is rich in serine residues of which theoretically some might be O-linked glycosylated. The occurrence of this type of glycans in 50 kDa human chitotriosidase has so far not been excluded or confirmed.

Please replace the paragraph on page 29, starting at line 6 with the following new paragraph:

The nucleotide sequence (SEQ ID NO:5) of the cDNA clone chi.39 shows an open reading frame that encodes an almost identical chitotriosidase protein with a total of 387 amino acids (see Fig. 2). After removal of the hydrophobic leader, the predicted protein for chi.39 cDNA has a length of 366 amino acids and expected molecular mass of 39 kDa. The signal peptide and the first 384 amino acids are identical to those in the chitotriosidase

protein encoded by the chi.50 cDNA. Only the 3 most C-terminal amino acids in the predicted 39 kDa chitotriosidase are distinct from those in the protein predicted for chi.50 cDNA.

Please replace the paragraph on page 33, starting at line 34 with the following new paragraph:

Figure. 1. Nucleotide sequence (SEQ ID NO:3) of chi.50 cDNA clone and predicted amino acid sequence (SEQ ID NO:4) of corresponding protein.

Please replace the paragraph on page 34, starting at line 4 with the following new paragraph:

Figure 2. Nucleotide sequence (SEQ ID NO:5) of chi.39 cDNA clone and predicted amino acid sequence (SEQ ID NO:6) of corresponding protein.

Please replace the paragraph on page 34, starting at line 23 with the following new paragraph:

The proteins are: human chitotriosidase (SEQ ID NO:7); a chitinase from the virus Autographa californica (GenBank L22858 (SEQ ID NO:8)); a chitinase from the tobacco hornworm Manduca sexta (GenBank U02270 (SEQ ID NO:9)); an endochitinase from the nematode Brugia malayi (Genbank M73689 (SEQ ID NO:10)); a human oviductal glycoprotein (GenBank U09550 (SEQ ID NO:11)); HCgp-39, a human glycoprotein produced by chondrocytes and synovial cells (GenBank M80927 (SEQ ID NO:12)); YM-1, a secretory protein of activated mouse macrophages (Pir S27879 (SEQ ID NO:13)); a chitinase from the fungus Aphanocladium album (SwissProt P32470 (SEQ ID NO:14)); a chitinase from the filamentous fungus Trichoderma harzianum (GenBank L14614 (SEQ ID NO:15)); chitinase A1 from the prokaryote Bacillus circulans (SwissProt P20533 (SEQ ID NO:16)); and a class V chitinase from the plant Nicotiana tabacum (GenBank X77110 (SEQ ID

NO:17)). Residues identical to chitotriosidase are indicated by the inverted characters. The proteins HCgp-39 and YM-1 are supposed to be not chitinolytic.